AMENDMENTS TO THE SPECIFICATION

Please delete four paragraphs added in the October 25, 2002 Amendment which replaced the four paragraphs beginning on page 8, line 28. And replace with the following new four paragraphs:

Figure 9B gives the nucleotide (SEQ. ID. NO: 39), complementary strand (SEQ. ID. NO: 41), and amino acid (SEQ. ID. NO: 40) sequence of the variable heavy chain domain of clone B38.

Figure 9C gives the nucleotide (SEQ. ID. NO: 42), complementary strand ~~(SEQ. ID. NO: 44)~~ (SEQ. ID. NO: 43), and amino acid ~~(SEQ. ID. NO: 43)~~ (SEQ. ID. NO: 34) sequence of the variable heavy chain domain of clone B18.

Figure 9D gives the nucleotide ~~(SEQ. ID. NO: 45)~~ (SEQ. ID. NO: 44), complementary strand ~~(SEQ. ID. NO: 47)~~ (SEQ. ID. NO: 45), and amino acid ~~(SEQ. ID. NO: 46)~~ (SEQ. ID. NO: 36) sequence of the variable heavy chain domain of clone B35.

Figure 9E gives the nucleotide ~~(SEQ. ID. NO: 48)~~ (SEQ. ID. NO: 46), complementary strand ~~(SEQ. ID. NO: 50)~~ (SEQ. ID. NO: 48), and amino acid ~~(SEQ. ID. NO: 49)~~ (SEQ. ID. NO: 47) sequence of the variable heavy chain domain of clone B04.

Please delete the paragraph added in the October 25, 2002 Amendment which replaced the second paragraph beginning on page 9, line 12. And replace with the following new paragraph:

Figure 11A shows the deduced amino acid sequence ~~(SEQ. ID. NOS: 51 and 53)~~ (SEQ. ID. NOS: 49 and 51) of recombinant antibody fragments specific for the factor VIII heavy chain. The amino acid sequence of germ line variable heavy chain gene segments DP10 (SEQ. ID. NO: 24) and DP47 ~~(SEQ. ID. NO: 52)~~ (SEQ. ID. NO: 50) is given. Deviations in amino acid sequence from these germline gene segments are indicated for two clones that encode recombinant antibodies that bind to the factor VIII heavy chain. Also the amino acid of the CDR3 and FR4 of the factor VIII heavy chain specific recombinant antibodies encoded by the two clones is given.

Please delete the paragraph added in the October 25, 2002 Amendment which replaced the third paragraph beginning on page 9, line 20. And replace with the following new paragraph:

Figures 11B and C give the nucleotide ~~(SEQ. ID. NOS: 54 and 57)~~ (SEQ. ID. NOS: 52 and 54), complementary strand ~~(SEQ. ID. NOS: 56 and 59)~~ (SEQ. ID. NOS: 53 and 55) and amino acid ~~(SEQ. ID. NOS: 55 and 58)~~ (SEQ. ID. NOS: 49 and 51) sequence of the variable heavy chain domain of two clones that encode recombinant antibodies that bind specifically to the factor VIII heavy chain.

Please delete the paragraph added in the October 25, 2002 Amendment which replaced the first paragraph beginning on page 28, line 16. And replace with the following new paragraph:

Next, different dilutions of scFv-EL14 and scFv-IT2 were tested for binding to immobilized factor VIII light chain as outlined above using CLB-CAg A as the detecting antibody (Figure 6). From this analysis it appeared that scFv-EL14 binds with a higher affinity to the factor VIII light chain than scFv-IT2. These results were complemented by immunoprecipitation experiments for scFv-EL14. Immunoprecipitation experiments employing a metabolically labelled fragment corresponding to the C2-domain was performed essentially as described previously (Fijnvandraat et al. 1998. Blood 91: 2347-2352). Monoclonal antibody 9E10 was covalently linked to CNBr-activated Sepharose 4B and this matrix was used to bind scFv-EL14. Specific binding of scFv-EL14 to metabolically labelled C2-domain was detected and this confirms the C2-specificity of this recombinant antibody fragment. In this example methods have been disclosed to characterize recombinant antibodies with specificity for the C2-domain. In examples 8 and 9, we describe the nucleotide and amino acid sequence of recombinant antibody fragments that bind specifically to the A2- ~~(SEQ. ID. NOS: 54-59)~~ (SEQ. ID NOS: 49 and 51-55) and A3-C1 ~~(SEQ. ID. NOS: 39-50)~~ (SEQ. ID. NOS: 34, 36 and 39-48) domain of factor VIII. The methods described in this example can easily be adapted by

an average expert skilled in the art, which will allow for characterization of recombinant antibodies directed against the A2 ~~(SEQ. ID. NOS: 54-59)~~ (SEQ. ID. NOS: 49 and 51-55), A3-C1 ~~(SEQ. ID. NOS: 39-50)~~ (SEQ. ID. NOS: 34, 36 and 39-48) or another epitope on factor VIII.

Please delete the paragraph added in the October 25, 2002 Amendment which replaced the first paragraph beginning on page 29, line 3, and ending on page 30, line 4. And replace with the following new paragraph:

In the previous example, we have shown that scFv-EL14 and scFv-IT2 bind to the factor VIII light chain and compete for binding with the murine inhibitory monoclonal antibody CLB-CAg 117. These observations suggest that the epitope of both scFv-EL14 and scFv-IT2 overlaps with that of CLB-CAg 117. It is expected that similar to CLB-CAg 117, scFv-EL14 and scFv-IT2 inhibit the biological activity of factor VIII. Increasing amounts of purified scFv's were tested for inhibition in the Bethesda assay. Surprisingly, addition of up to 170 μg/ml scFv did not result in factor VIII inhibition as measured in the Bethesda assay. In contrast, CLB-CAg 117 readily inhibited factor VIII when measured in the same assay. Apparently, binding of scFv-EL14 and scFv-IT2 to factor VIII does not interfere with the biological activity of factor VIII. This finding prompted us to investigate the capacity of both scFv-EL14 and scFv-IT2 to overcome inhibition by CLB-CAg 117. Monoclonal antibody CLB-CAg 117 was diluted till a final inhibitory activity of 2 BU/ml. This value corresponds with a residual factor VIII activity of 25% in the Bethesda assay. Subsequently, increasing concentrations of scFv-EL14 and scFv-IT2 were added. Surprisingly, both scFv-EL14 and scFv-IT2 could overcome the factor VIII inhibitory activity of CLB-CAg 117 (Figure 7). ScFv-14 (panel A) proved to be more efficient than scFv-IT2 (panel B) in neutralizing the inhibitory activity of CLB-CAg 117. Both scFv-EL14 and scFv-IT2 were unable to neutralize the inhibitory activity of monoclonal antibody CLB-CAg A, directed against amino acid residues Glu^{1811}-Lys^{1818} on the factor VIII light chain (Lenting et al. 1996. J. Biol. Chem. 271:1935-1940). These results for the first time show that antibody fragments with factor

VIII specificity can be used to interfere with the activity of factor VIII inhibitors. Administration of these antibody fragments will be beneficial for the treatment of patients with inhibitory antibodies directed against factor VIII. In this example the biological activity of antibody fragments with C2-specificity is disclosed. In examples 8 and 9, the nucleotide and amino acid sequence of recombinant antibody fragments that bind to the A2 ~~(SEQ. ID. NOS: 54-59)~~ (SEQ. ID. NOS: 49 and 51-55) and A3-C1 ~~(SEQ. ID. NOS: 39-50)~~ (SEQ. ID. NOS: 34, 36 and 39-48) domain of factor VIII is disclosed. The methods disclosed in this and the previous example can easily be adapted by an average expert skilled in the art to establish the capacity of recombinant antibody fragments directed against the A2 or A3-C1 domain to neutralize factor VIII inhibitors. Similar to outlined in this example recombinant antibody fragments that bind to other regions can be evaluated for their neutralizing capacity of factor VIII inhibitors. Similarly to what has been described in this example for scFv-EL14 and scFv-IT2, antibody fragments binding to A2, A3-C1 and other domains on factor VIII can be used for treatment of patients with factor VIII inhibitors.

Please delete the paragraph added in the October 25, 2002 Amendment which replaced the second paragraph beginning on page 32, line 21. And replace with the following new paragraph:

The nucleotide sequence of the variable heavy chain fragments of 26 clones that reacted specifically with recombinant A3-C1 domain was determined essentially as described in Example 4. The sequences obtained were aligned with heavy chain sequences in the database "V BASE" of the MRC Centre of Protein Engineering (Cambridge, UK). The 26 clones analyzed were encoded by four different VH-gene segments DP15 (SEQ. ID. NO: 31), DP31 (SEQ. ID. NO: 33) and DP49 (SEQ. ID. NO: 35) and DP77 (SEQ. ID. NO: 37). The amino acid sequence of the variable heavy chain fragments of clones B38 (SEQ. ID. NO: 32), B18 (SEQ. ID. NO: 34), B35 (SEQ. ID. NO: 36) and B04 (SEQ. ID. NO: 38) is listed in Figure 9A. The nucleotide sequence of

these four clones is presented in Figures 9B-E ~~(SEQ. ID. NOS: 39, 42, 45, 48)~~ (SEQ. ID. NOS: 39, 42, 44 and 46).

Please delete the paragraph added in the October 25, 2002 Amendment which replaced the second paragraph beginning on page 34, line 33, and ending on page 35, line 4. And replace with the following new paragraph:

The nucleotide sequence of the variable heavy chain fragments of 26 clones that reacted specifically with the factor VIII heavy chain were determined essentially as described in Example 4. The sequences obtained were aligned with heavy chain sequences in the database "V BASE" of the MRC Centre of Protein Engineering (Cambridge, UK). The 26 clones analyzed were encoded by two different VH-gene segments DP10 (SEQ. ID. NO: 24) and DP47 ~~(SEQ. ID. NO: 52)~~ (SEQ. ID. NO: 50) (Figure 11A). The nucleotide sequence of the variable heavy chain of these clones is listed in Figure 11B ~~(SEQ. ID. NO: 54)~~ (SEQ. ID. NO: 52) and C ~~(SEQ. ID. NO: 57)~~ (SEQ. ID. NO: 54).

Please insert the attached paper copy of the Sequence Listing at the end of the specification.